# 5 Minute JournalClub

**POST-ASH** Issue 7, 2014

# ASH 2013 Highlights with Novel Therapeutic Agents in AML

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## CME INFORMATION

## OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on chimeric antigen receptor T-cell therapy for leukemia and lymphoma from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

## LEARNING OBJECTIVES

- Develop an understanding of the mechanism of action of chimeric antigen receptor T-cell therapy, and evaluate the emerging efficacy and safety data with this therapeutic approach under evaluation in the front-line and relapsed/refractory settings for B-cell lymphoma and leukemias.
- Evaluate the benefits and risks of the addition of gemtuzumab ozogamicin to standard chemotherapy and of other emerging agents such as novel FLT3 inhibitors or hypomethylating agents for the treatment of acute myeloid leukemia.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Hagop M Kantarjian, MD
Chairman and Professor, Leukemia Department
The University of Texas MD Anderson Cancer Center
Houston, Texas

No real or apparent conflicts of interest to disclose.

David L Porter, MD
Abramson Cancer Center
University of Pennsylvania Health System
Jodi Fisher Horowitz Professor of Leukemia Care Excellence
Director, Blood and Marrow Transplantation
Philadelphia, Pennsylvania

Contracted Research: Novartis Pharmaceuticals Corporation; Other Remunerated Activities: Genentech BioOncology (faculty and spouse).

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: May 2014
Expiration date: May 2015

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POST-ASH Issue 7, 2014

To go directly to slides and commentary for this issue, **click here**.

On this final issue of our review of select key papers presented at the American Society of Hematology annual meeting, we focus on a handful of fascinating early clinical reports on CART and a smattering of what's new in AML.

**CART clinical trial data**

David L Porter, MD

Although we heard about the seemingly miraculous effects of this novel therapeutic approach in 2012 in Atlanta, New Orleans was the true coming out party for CART-based approaches, specifically those targeting CD19. Led by the powerhouse team at the University of Pennsylvania, which includes Dr David Porter, we were treated to numerous fascinating presentations that have generated great excitement and enthusiasm.

Since ASH I have been fortunate enough to interview Dr Porter on 2 occasions (**click for audio**), and it is impossible to hear about this dramatic story without getting goose bumps.

The concept behind Penn's CART-based approach is intriguing. Patients undergo leukapheresis, after which their T-cells are transduced with a lentivirus encoding an anti-CD19 single-chain variable fragment linked to 4-1BB and CD3-ζ signaling domains. The genetically modified cells are then expanded ex vivo, and soon after a course of lymphocyte-depleting chemotherapy they are then reinfused into the patient where, as documented previously and in new reports at ASH, they expand (up to 10,000-fold), persist functionally (beyond 3 years) and exert a direct antitumor effect.

Early efforts by the group have focused on very advanced chronic lymphocytic leukemia (CLL) and B-cell acute lymphoblastic leukemia (ALL), and although they hoped to see some discernible benefit in early testing, as related by Dr Porter, the initial clinical responses were stunning in rapidity and depth. Much of this work was updated and expanded on in New Orleans. Dr Stephan Grupp **presented longer follow-up outcomes** from 17 adults and children with relapsed/refractory ALL revealing that 82% achieved a complete response (CR). Similarly, Dr Porter **provided an update** from their Phase I study in which 8 of 14 patients with extensively pretreated CLL had objective responses, including 4 patients with CRs, none of whom have yet experienced

relapse. He also unveiled data from their dose-finding randomized Phase II study demonstrating that 7 of 18 patients responded, including 3 CRs, with no correlation between dose and outcome or toxicity.

Perhaps the highlight of these presentations, at least in my mind, was an impressive set of scans that Dr Porter displayed from a patient with del(17p) CLL treated on their original pilot study. Amazingly, 3 months after receiving the CART infusion this individual, whose disease had progressed through 10 prior therapies, including ibrutinib and radiation therapy, was pretty much disease free in peripheral blood and bone marrow.

In discussing this work with Dr Porter, I was eager to learn more about the profound and rapid tumor lysis/cytokine release syndrome (CRS) that has been described with this therapy. I was wide-eyed as he detailed the team's early experiences with this scary complication that generally occurred within the first few weeks of treatment at the peak of initial T-cell expansion and initially led to life-threatening multiorgan failure. What was perhaps most compelling was that the team was able to quickly determine that the key cytokine causing this syndrome was IL-6, and they were able to successfully intervene with a novel IL-6 receptor antibody approved for rheumatoid arthritis (tocilizumab).

Penn is not alone at the forefront of this research, and at ASH the Memorial group also reported activity with a slightly different anti-CD19 CAR platform across several diseases. In high-risk CLL, Dr Jae Park **presented preliminary data** from a Phase I study evaluating this approach as consolidation after up-front rituximab-chemotherapy. While the data set was quite small — 8 patients with 2 CRs and 2 partial responses — it provides an important proof of principal that ultimately may allow some patients with CLL to receive a short-term treatment that will lead to prolonged tumor control. Relevantly, the study results suggest greater benefit in patients with lower tumor burden, and Dr Porter believes that an important future strategy will be initial cytoreduction, particularly with novel B-cell inhibitors like ibrutinib, followed by an attempt at cure with CART.

Memorial's Dr Marco Davila **also reported** on CAR therapy as a bridge to allotransplant in patients with B-cell ALL, including those with Philadelphia chromosome-positive disease. Importantly, responses were rapid, occurring as early as 7 to 14 days, CRS was manageable and 10 of 12 patients with detectable disease before CAR therapy became minimal residual disease-negative. Four patients went on to allotransplant with 5 more being prepped for it.

The NCI, too, is very involved in this field, and at ASH they provided us with more data on the **use of this technology in ALL** as well as our **first look at it in B-cell lymphomas**, where 5 of 8 patients with chemotherapy-refractory diffuse large B-cell lymphoma or primary mediastinal B-cell lymphoma experienced objective tumor responses.

The next step for this fascinating and innovative treatment strategy is to not only obtain more data but also to investigate the feasibility and reproducibility of doing this on a larger-scale basis.

## AML: Life beyond 3 plus 7

The dismal current landscape of this important cause of mortality is reflected by the fact that the only compound approved for this disease in the last 20 years, gemtuzumab ozogamicin (GO), was removed from the market by the FDA 4 years ago due to toxicity concerns.

As such, for far too long conversations about AML management have revolved around optimal induction and consolidation chemotherapy doses and schedules and the role for various transplant strategies. However, the rapidly emerging translational and related clinical science that permeates ongoing AML research has many optimistic that brighter days are ahead (**click for summary slides of studies discussed below**).

One of the more talked about areas is management of the 30% of patients with FMS-like tyrosine kinase 3 (FLT3) mutations, and in the Big Easy Dr Jorge Cortes presented a provocative study on the effects of the as yet unapproved FLT3 inhibitor quizartinib. One of the proposed benefits of this agent is that it is more specific for the target than tyrosine kinase inhibitors such as sorafenib, which is sometimes employed off label when no other alternatives exist. In this Phase II study using lower doses of quizartinib in 76 patients, a 47% CR rate with acceptable toxicities was reported. All eyes are on the ongoing Phase III study evaluating this compound in hopes that it may end up as a useful tool in practice.

The MD Anderson group also reported on SGI-110 — a novel molecule that combines decitabine with guanosine to produce a longer half-life and potentially higher areas under the curve than decitabine. Importantly, in this Phase II study this subcutaneously administered hypomethylating agent resulted in an encouraging preliminary objective response rate of 53% in elderly patients with treatment-naïve AML. Dr Hagop Kantarjian and his group at MD Anderson are interested in doing a study comparing this agent to conventional decitabine or azacitidine.

Because activating KIT mutations are present in 25% to 30% of patients with core binding factor (CBF) AML, it has been hypothesized that KIT inhibition might provide therapeutic benefit. In this regard, the CALGB reported on a single-arm trial evaluating the addition of dasatinib to induction chemotherapy in patients with molecular confirmation of CBF AML. Reported at ASH, the trial resulted in an encouraging CR rate of 92% in 59 evaluable patients, but many are reserving judgment about this approach until further follow-up is available.

Given its activity in a multitude of hematologic cancers, it should probably come as no surprise that lenalidomide is also being evaluated in AML. Significantly, preliminary results look encouraging with a CR rate of 43% in 37 elderly patients over age 70 with low-dose lenalidomide added to low-dose Ara-C (LDAC). Perhaps even more importantly, a 5-gene molecular signature has been identified that appears highly predictive of treatment response with 87% overall accuracy.

Additionally, although the previously mentioned anti-CD33 antibody-drug conjugate GO is no longer available, at ASH we saw data reinforcing its evidence-based benefit most

specifically for patients with CBF AML. Described in **a meta-analysis, a pediatric study and a longitudinal analysis** of trials of the UK MRC/NCRI group, these results all point to a modest advantage with limited toxicity. Whether GO will make it back into the clinic, however, remains unclear.

Finally, in terms of the FDA and AML, one of the more interesting and positive recent developments from the agency has been the 2012 implementation of the "Breakthrough Therapy" designation pathway, which fast-tracks promising agents in diseases with important unmet needs. Over the past year on our CME programs we have discussed many exciting oncology compounds that have earned this designation, and just 2 weeks ago we saw this novel pathway in action as the second-generation ALK inhibitor ceritinib was granted accelerated approval in ALK-positive non-small cell lung cancer based on the results of a single-arm, open-label clinical trial enrolling 163 patients.

Last fall, the selective and potent polo-like kinase (PLK) inhibitor volasertib became the only "AML drug" to join this short "Breakthrough" list. Volasertib inhibits PLK1 — the best characterized of the 5 known human PLKs and a critical enzyme regulating mitosis — resulting in cell cycle arrest and ultimately cell death (apoptosis). At ASH 2012 a randomized Phase I/II trial reported an impressive response rate advantage when the agent was added to LDAC in patients not eligible for intensive induction. These encouraging results led to the ongoing Phase III POLO-AML-2 trial with a similar randomization in patients age 65 or older with previously untreated AML not eligible for intensive induction. Although the future of this interesting agent is unclear, it seems plausible that in the next few years AML will join the other myeloid cancers in seeing the documented benefit of important new and clinically useful treatment strategies based on the evolution of understanding the underlying disease biology.

This concludes our ASH review series. If you're heading to Chicago this month, join us at the end of each day for a series of evening symposia as we review what's happening in **lung cancer**, **gastrointestinal cancers**, **non-Hodgkin lymphoma/multiple myeloma** and **HER2-positive breast cancer**.

Neil Love, MD
**Research To Practice**
Miami, Florida

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# ASH 2013 Highlights with Novel Therapeutic Agents in AML

## Presentations discussed in this issue

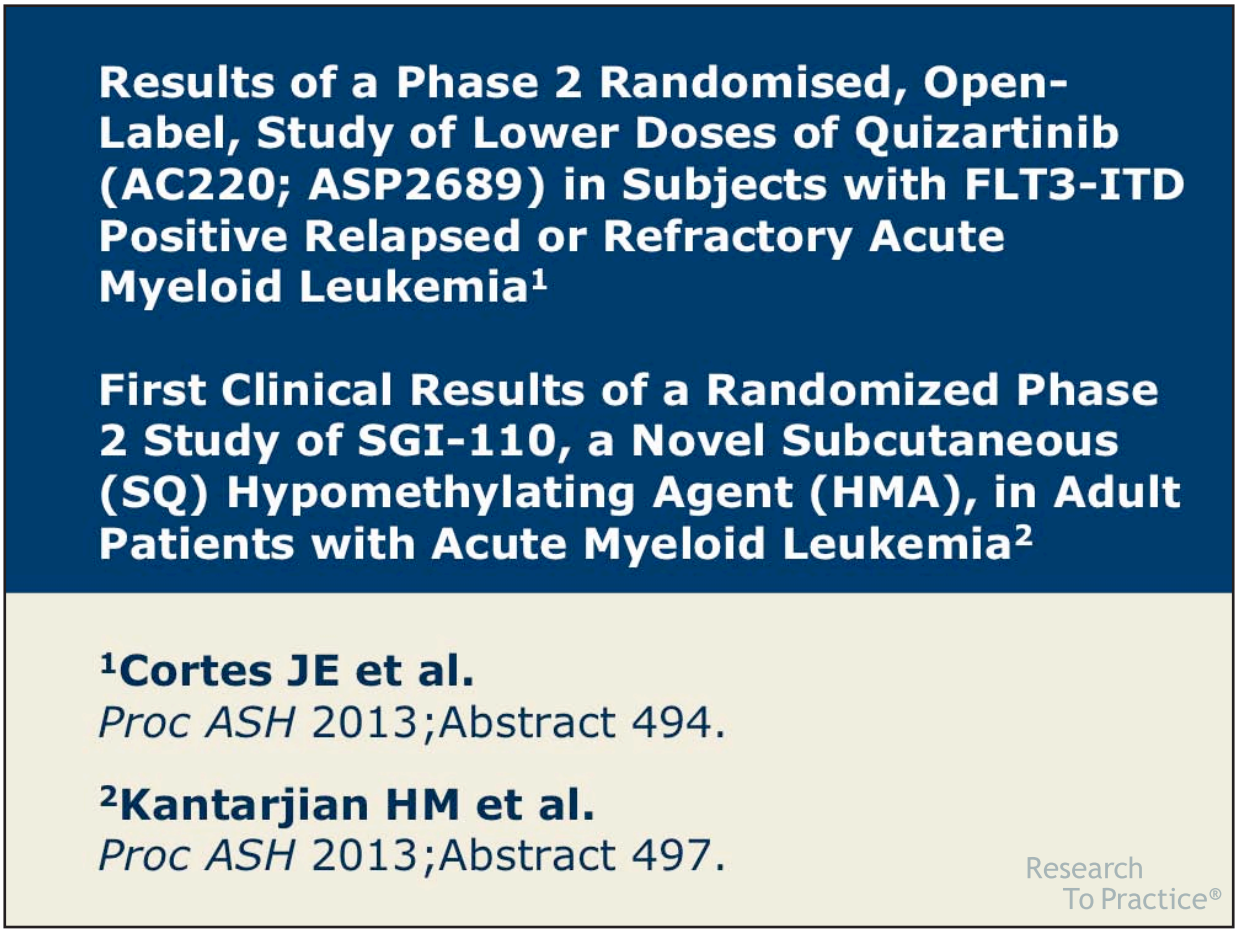
Cortes JE et al. **Results of a phase 2 randomized, open-label, study of lower doses of quizartinib (AC220; ASP2689) in subjects with FLT3-ITD positive relapsed or refractory acute myeloid leukemia (AML).** *Proc ASH* 2013;**Abstract 494**.

Kantarjian HM et al. **First clinical results of a randomized phase 2 study of SGI-110, a novel subcutaneous (SQ) hypomethylating agent (HMA), in adult patients with acute myeloid leukemia (AML).** *Proc ASH* 2013;**Abstract 497**.

Marucci G et al. **Adding the KIT inhibitor dasatinib (DAS) to standard induction and consolidation therapy for newly diagnosed patients (pts) with core binding factor (CBF) acute myeloid leukemia (AML): Initial results of the CALGB 10801 (Alliance) study.** *Proc ASH* 2013;**Abstract 357**.

Visani G et al. **Low-dose lenalidomide plus low dose cytarabine induce complete remission that can be predicted by genetic profiling in very elderly acute myeloid leukemia patients.** *Proc ASH* 2013;**Abstract 496**.

## Slides from presentations at ASH 2013 and transcribed comments from a recent interview with Hagop M Kantarjian, MD (1/29/14)



**Adding the KIT Inhibitor Dasatinib (DAS) to Standard Induction and Consolidation Therapy for Newly Diagnosed Patients (pts) with Core Binding Factor (CBF) Acute Myeloid Leukemia (AML): Initial Results of the CALGB 10801 (Alliance Study)[3]**

**Low-Dose Lenalidomide plus Low-Dose Cytarabine Induce Complete Remission That Can Be Predicted by Genetic Profiling in Very Elderly Acute Myeloid Leukemia Patients[4]**

[3]**Marucci G et al.**
*Proc ASH* 2013;Abstract 357.

[4]**Visani G et al.**
*Proc ASH* 2013;Abstract 496.

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**Results of a Phase 2 Randomised, Open-Label, Study of Lower Doses of Quizartinib (AC220; ASP2689) in Subjects with FLT3-ITD Positive Relapsed or Refractory Acute Myeloid Leukemia**

**Cortes JE et al.**
*Proc ASH* 2013;Abstract 494.

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# Comparison of Lower-Dose Quizartinib to Higher Doses

| | 2689-CL-2004 | | AC220-002 (cohort 2) | | |
|---|---|---|---|---|---|
| | 30 mg/ day (n = 38) | 60 mg/ day (n = 38) | 90 mg/ day (n = 57) | 135 mg/ day (n = 67) | 200 mg/ day (n = 12) |
| **Best response** | | | | | |
| CRc rate | 47% | 47% | 47% | 45% | 42% |
| PR rate | 13% | 24% | 25% | 28% | 50% |
| **Maximum change in QTcF from baseline (msec)** | | | | | |
| ≤30 | 50% | 44% | 9% | 9% | 0% |
| >30 to ≤60 | 47% | 36% | 46% | 51% | 8% |
| >60 | 3% | 19% | 46% | 39% | 92% |

CRc rate = complete remission (CR) + CR with incomplete platelet recovery + CR with incomplete hematologic recovery

Cortes JE et al. *Proc ASH* 2013;Abstract 494.

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# Results Summary

- Sustained efficacy and decreased QT signal with lower doses of quizartinib
  - Efficacy:
    - Substantial activity at both doses
  - Safety:
    - Similar safety profile at 30- and 60-mg doses
    - QTcF prolongation is dose-dependent. QTcF at both doses was decreased compared to prior Phase II study at 90 mg/day and 135 mg/day.
- Next step:
  - Global Phase III randomized trial of quizartinib in patients with FLT3-ITD-positive disease in first relapse is under way (NCT02039726).

Cortes JE et al. *Proc ASH* 2013;Abstract 494.

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# First Clinical Results of a Randomized Phase 2 Study of SGI-110, a Novel Subcutaneous (SQ) Hypomethylating Agent (HMA), in Adult Patients with Acute Myeloid Leukemia

**Kantarjian HM et al.**
*Proc ASH* 2013;Abstract 497.



## Results Summary

- SQ SGI-110 is a new HMA that is well tolerated and clinically active in the treatment of AML.
- Complete remissions and potent demethylation of ≥10% were equally observed at the doses of 60 and 90 mg/m$^2$.
- These data support further Phase III investigation of this agent in the treatment of AML.
- Preliminary overall remission rate of 53% in treatment-naïve elderly AML seems to compare favorably to previous results reported for HMA treatment, but this result needs confirmation in a larger number of patients and randomized studies.

Kantarjian HM et al. *Proc ASH* 2013;Abstract 497.

**Investigator Commentary: First Clinical Results of a Phase II Study of the Novel Hypomethylating Agent SGI-110**

SGI-110 is a molecule that combines decitabine with guanosine, so this drug can produce higher areas under the curve for the release of decitabine and has a longer half-life. This was an update of a study with SGI-110. From my own impression and from the studies reported, SGI-110 is a drug to be reckoned with in terms of its further evaluation with pivotal trials that compare SGI-110 to either azacitidine or decitabine in the setting of myelodysplastic syndrome or AML. This is a drug to keep in mind, and I do believe it is going to be a significant drug in the future based on the published data so far.

***Interview with Hagop M Kantarjian, MD, January 29, 2014***



# Adding the KIT Inhibitor Dasatinib (DAS) to Standard Induction and Consolidation Therapy for Newly Diagnosed Patients (pts) with Core Binding Factor (CBF) Acute Myeloid Leukemia (AML): Initial Results of the CALGB 10801 (Alliance Study)

**Marucci G et al.**
*Proc ASH* 2013;Abstract 357.

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## Results Summary

- Early results from this study show:
  - Rapid diagnostic screening for CBF AML is feasible within a cooperative group
  - DAS plus chemotherapy in patients with CBF AML is tolerable, including in older patients
  - Initial clinical outcomes are at least comparable to those historically observed in this patient population
    - CR rate = 92%
    - 1-year OS rates: 95% (younger patients) and 62% (older patients)
- Patient follow-up and molecular characterization are ongoing and will be correlated with toxicity and clinical outcome.

Marucci G et al. *Proc ASH* 2013;Abstract 357.



# Low-Dose Lenalidomide plus Low-Dose Cytarabine Induce Complete Remission That Can Be Predicted by Genetic Profiling in Very Elderly Acute Myeloid Leukemia Patients

**Visani G et al.**
*Proc ASH* 2013;Abstract 496.

# Results Summary

- Low-dose lenalidomide (10 mg/day) plus low-dose cytarabine has high clinical activity in elderly patients with AML, with an overall CR rate of 43%.
  - 9 of 16 responding patients are still in CR after median follow-up of 12 months
  - Responding patients had a longer median overall survival than nonresponders (428 versus 74 days)
- A molecular signature including 114 genes and 18 microRNA was identified as being associated with clinical response (CR versus no CR).
- Based on the expression of 5 genes, an algorithm was developed to predict treatment response that was validated by showing 87% overall accuracy.

Visani G et al. *Proc ASH* 2013;Abstract 496.

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